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Design, Development and evaluation of emulgel for topical drug delivery

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1. Abstract of proposed work:

Recently use of micro- emulsion based gel as a vehicle for delivery of BCS class II & III drug through topical drug delivery has been increased. The purpose of present study was to develop a micro- emulsion based gel formulation and characterize for topical drug delivery through nail and skin. Spontaneous emulsification technique i.e water titration method is used for preparation of micro-emulsion. The prepared micro-emulsion is characterized for Globule size, zp, PDI, pH, percentage of transmittance (%T), Drug content, thermodynamic stability, dilution test, TEM etc. After addition of required amount of gelling agent to micro- emulsion it gets converted into gel. These prepared micro-emulsion based gel is evaluated for physical appearance, Ph, spread ability, drug content and drug release study. Optimization of formulation is done by selecting appropriate parameters. Stability, skin irritation and animal study of optimized formulation will be done.

KEYWORDS: Emulgel, nail intecton, micro-emulsion based gel, drug release , optimization, stability and safety study.

1. Introduction:

The body normally hosts a variety of microorganisms, including bacteria, viruses, and fungi. Some of these are useful to the body and others cause infections. Fungi can live on the skin, burn wound, dead tissues of the hairs, nails. Continuous exposal of nail to warm, moist environments usually develops nail infection. Fungal infection to the skin and nail is most common and live long lasting if unproperly treated[1,2].

Nail are the complex structure composed of nail bed, nail matrix, nail folds and outer layer nail plate. The nail plate contains 80-90 layers of dense keratinized dead cells, with desmosome unions. This structure protects nail form external damage. Nail folds are attach to nail matrix and are continuation of skin, developing the cuticle which seals the nail surface, preventing the entrance of chemical and microorganism. Nail plate is main route for penetration of drug[3]. Nail growth occurs from the nail matrix, the epithelium beneath the nail root, through the transformation of superficial cell into nails cells i.e. growth rate of nail is very slow because of is infection remain at this site for longer days. The most common diseases affecting the nail unit are onychomycosis (fungal, bacterial), psoriasis of the nails, onychtrophia, leucoychia, onychogryposis etc [4].

Some factors responsible for transport of drug through nail are molecular size drug, hydophilicity / lipophilicity of dug, nature of vehicle, ph of vehicle. Recently more focus of study is on enhancing drug permeation through nail plate[5,6]. Physical, chemical and mechanical methods have been used to decrease the nail barrier. Within each of these broad categories, many techniques exist to enhance penetration. Mechanical modes of penetration enhancement are typically straightforward, and have the most in vivo experience associated with them[1,7]. In contrast, many of the chemical and physical methods discussed are still in the in vitro stages of development; laboratory studies are currently examining these techniques using human nail samples. The goal of topical therapy for onychomycosis is drug penetration into deep nail stratums at amounts above the minimal inhibitory concentration[8,9]. Chemical and physical modes of penetration enhancement may improve topical efficacy. Varity of conventional formulation like gel, cream, ointment, solution, nail lacquer and also oral antifungal are available for treatment of nail infection.

The major hurdle associated with developing nail lacquers treatment for nail disorders is to deliver the API therapeutically effective concentrations to the site of infection, which is often under nail [10]. However possible means to enhance nail penetration must be explored in greater depth before effective local treatments for fungal nail infections are develop. Penetration of topical antifungal through the nail plate requires a vehicle that is specifically formulated for transungual delivery [12,13]. The success of topical therapy to nail is depend on achievement of effective MIC in the nail plate; therefore, a suitable antifungal drug must couple with an appropriate delivery method[14].

Micro-emulsions is defined as nano sized transparent, isotropic, thermodynamically more stable formulation comprising of oil, surfactant, co-surfactant and water[15,16]. Concentration of Smix is more in microemulsion as compare to nanoemulsion. Microemulsion offers certain advantages over nanoemulsion such as they are more stable, easy to formulate, low energy is required, high drug loading etc[17]. As microemulsion have low viscosity it can't retains long time at the infected site so, it is converted into gel. This newly formed system is called as microemulsion based gel which prolong the contact time of formulation with applied surface, apart from that many BCS class II & III which cannot be incorporated directly into aqueous gel base due to solubility imitation, an emulgel formulation can over this problem[18].

Nano sized emulsion based gel (microemulgel) gives more advantages over topical gel, cream, lotion, solution such as they are less sticky, easy to remove, easy to spread, better drug entrapment, increased permeability, better stability, sustained release. The goal of our research is to formulate topical microemulsion based gel with desirable characteristics and enhanced transungual permeability through the nail and various skin infection. optimized microemulsion based gel is evaluated for drug release, skin irritation along with stability studies for its safe and effective topical use.

REVIEW OF LITRETURE :

1. **Purva Thatai et al** (2017)
   The present study was aimed to optimize, develop, and evaluate microemulsion and microemulsion-based gel as a vehicle for transungual drug delivery of terbinafine hydrochloride for the treatment of onychomycosis. D-optimal mixture experimental design was adopted to optimize the composition of microemulsion having amount of oil (X 1), Smix (mixture of surfactant and cosurfactant; X 2), and water (X 3) as the independent variables. The formulations were assessed for permeation (micrograms per square centimeter per hour; Y 1), particle size (nanometer; Y 2), and solubility of the drug in the formulation (milligrams per milliliter; Y 3). The microemulsion-based gel showed better penetration (∼5 folds) as well as more retention (∼9 fold) in the animal hoof as compared to the commercial cream. The techniques used to screen penetration enhancers (hydration enhancement factor, ATR-FTIR, SEM, and DSC) revealed the synergistic effect of combination of urea and n-acetyl cysteine in disruption of the structure of hoof and hence, leading to enhanced penetration of drug.[19]
2. **Quamrul Hoda et al. 2021**
   The objective of the present study was to prepare valencene (sesquiterpene) containing invasomes for itraconazole (ITZ) transungual delivery using central composite design. The antifungal activity of optimized formulation was screened against Trichophyton rubrum, a common causative onychomycosis pathogen, by cup plate method. The optimized ITZ-loaded invasomes formulation evaluated for vesicles size, entrapment efficiency and in vitro drug release. The ITZ-loaded invasomes gel formulation evaluated for homogeneity, pH, viscosity, drug content, Spreadability and extrudability. The ITZ-loaded invasomes gel presented 71.11 ± 3.65% cumulative permeation of drug via goat hooves. The in vitro antifungal activity depicted that the ITZ-loaded invasomes gel and marketed preparation were presented zone of inhibition of 21.42 mm and 10.64 mm against T. rubrum respectively. Hence the prepared ITZ-loaded invasomes formulation could therefore be a promising topical dosage to mitigate the indications and hasten the cure for onychomycosis than conventional available therapies[11].
3. **Vikas Agrawal et al.. 2021**
   The onychomycosis treatment remains a big challenge for onychologist due to the shorter nail residence time of topical formulations and the lack of availability of novel formulations in markets for new generation antifungal drugs. The objective of this work was to design, develop, optimize, and evaluate microemulsion formulations for effective delivery of efinaconazole through transungual route in onychomycosis treatment. Capmul® MCM (Glyceryl Caprylate/Caprate) as oil, Labrasol® (caprylocaproyl polyoxyl-8 glycerides) as a surfactant, and Transcutol® P (diethylene glycol monoethyl ether) as co-surfactant exhibited higher solubility of efinaconazole and surfactant-cosurfactant mixture (Smix) in a ratio of 1:1 rendered higher microemulsion region in the pseudo-ternary phase diagram. The optimized microemulsion formulation globule size

was less than 100 nm. The ex vivo permeation confirmed improved permeation of efinaconazole from microemulsion formulations in comparison to reference formulation without observing any lag in drug permeation through the nail plate. The in vitro antifungal study data indicated increased antifungal efficacy relative to efinaconazole topical solution against Trichophyton rubrum, Trichophyton mentagrophytes, and Candida albicans species. Further, an in vitro cell cytotoxicity study exhibited no toxic effect for any excipients used in the formulation while applied on nail cell[16].

4. **Arjune Raj R et al 2020**

   The objective of the work was to formulate nail lacquer containing fluconazole an antifungual drug for the treatment of onychomycosis. Topical and ungual therapy is limited because of the poor permeation of the drug through nail plate. Film base was prepared using varying concentration of cellulose acetate and ethyl cellulose as polymers. The permeation enhancers were screened by nail plate hydration. The formulation was optimized using Box-Behnken design. Various physicochemical parameters like nonvolatile content, drying rate, gloss, smoothness to flow, % CDR for nail lacquer was analyzed out. Zone of inhibition and drying time was in range with the standard. Antifungal nail lacquer with suitable permeation enhancers are far better for the treatment of onychomycosis than cream, gel and solutions. The high permeation rate helps to reduce the treatment period[2].

5. **B.S. Parejiya et al 2019**

   Aim of present study is to prepare, evaluate Microemulsion-based gel of terbinafine for the treatment of onychomycosis. optimization of formulation was done using D-optimal design. Comparative study of prepared formulation with marked cream was done. Microenulasion based gel formulation have more drugs release and more zone of inhibition than marketed formulation[7].

6. **Agrawal V, et al 2021**

   Aim of present study is to Design and evaluation of microemulsion-based efinaconazole formulations for targeted treatment of onychomycosis through transungual route: Ex vivo and nail clipping studies. In study it was concluded that microemulsion based gel are the promising drug delivery system for transungual drug delivery[16] .

7. **Pooja V Torambe 2023**

   Aim of present is to optimize microemulsion-based gel of ciprofloxacin hydrochloride BCS Class IV to increase its solubility and permeability through the cutaneous layer for targeting bacterial skin infections. Solubility analysis suggested tween 80, oleic acid and propylene glycol for the formulation of microemulsion. To depict the microemulsion formulation pseudo ternary phase diagram was employed. %Transmittance, zeta potential, dissolution study and size analysis were carried out for evaluation of microemulsion. 3^2 factorial design was used. Two variables i.e concentration of Sepineo P600 and Carbopol 934 effect on microemulgel was evaluated. Evaluation of gel was carried for physical parameters, antimicrobial, in-vitro and ex-vivo release study. The

obtained results exhibited that the permeability and bioavailability of the drug was increased when given through a topical route[20].

8. **Swati jagadale et al 2020**

Aim of study is to design controlled release topical delivery of mupirocin for treatment of skin infection. Mupirocin is an antibacterial drug. It is also used for treatment of inflammation of a hair follicle. Half -life of mupirocin is only 20-40 min. It has very slight solubility in water. Patent literature had shown work on ointment, antibiotic composition, nasal and topical composition. Emulgel is a duel control release system for topical delivery of hydrophobic drugs. Objective was to formulate emulgel with controlled delivery of mupirocin using Sepineo P 600. Soya oil, tween 80 and polyethylene glycol 400 (Oil: Surfactant: Cosurfactant) was used for emulsion formulation. Emulgel was optimized by factorial design. Emulgel was evaluated for its physical characterization, in-vitro release, ex-vivo release, antimicrobial and anti-inflammatory study. Release studies indicated controlled release of drug form Sepineo P600 gel due to its higher gelling capacity. Comparative study was done with marketed formulation. Conclusion Antimicrobial and anti-inflammatory study proved successful development of stable controlled release mupirocin emulgel[12].

OBJECTIVE OF RESEARCH:

Design, Development and Evaluation of antimicrobial agent loaded nano sized emulgel for topical drug delivery

Objective:

- To improve the bioavailability of drug.
- To improve drug loading.
- To prolong the release over predetermined time period.
- To perform drug release study.
- To optimize emulgel formulation.
- To perform stability study and skin irritation study for safety us of optimized formulation.

Methodology to be adopted:

1. Literature survey
2. Selection and collection of Drug and excipient
   Drug: Antifungal, Antibacterial etc
3. Selection of excipient: oil, surfactant, co-surfactant , gelling agent, penetration enhancer etc
4. Experimental work:
   a. Pre formulation studies:
      - Procurement of drug
      - Evaluation of organoleptic properties
      - Solubility study of drug in oil &Smix
      - Melting point of drug
      - Determination of max absorbance of drug
      - FTIR analysis
      - Differential scanning calorimetry (DSC)
   b. Drug excipient compatibility study
   c. Construction of pseudo ternary phase diagram
   d. Preparation and evaluation of micro- emulsion
      - Globule size
      - PDI
      - ZP
      - % transmittance
      - Drug content
      - Thermodynamic stability: phase separation, heating cooling cycle
      - TEM
   e. Preparation and evaluation of prepared microemulsion based gel
      - Physical appearance
      - Spreadability
      - Drug content
      - In-vitro drug release
      - Transungual permeation through animal hooves
   f. Evaluation of optimized batch of formulation.
   g. Detection of antimicrobial activity.
   h. Skin irritation study
   i. Stability study of optimized formulation.

Significance of the study:

Microemulsion based gel possesses both beneficial characteristic of microemulsion and gel in one formulation for topical application. Microemulsion act as beast vehicle for both BCS class II & IV. Microemulsion based gel have better loading capacity than other nano carriers. Method of preparation of microemulsion is more easy and less energy is required for formulation as compare to nano emulsion. They have more stability, low skin irritation, increase drug release for topical delivery as compare to liposomes. Neosomes, nanoparticles etc.

Year Wise Plan of Work And Target To Achive

Present study is designed in a such way that it will come to a conclusive outcome within 03 years from the date of allocation. The year wise plan is as following

First year

- Literature survey
- Selection and collection of drug and excipient
- Preformulation study

Second year

- Design, development and evaluation of emulgel
- Safety and efficacy study optimized batch of formulation

Third year

- Statistical analysis, Data Interpretation and Conclusion
- Publication of research work and submitting data.

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